Supplementary material: contents

TACKLING ACUTE KIDNEY INJURY - A MULTI-CENTRE QUALITY IMPROVEMENT PROJECT

Primary Contact	Dr Nick Selby Associate Professor of Nephrology and Honorary Consultant nicholas.selby@nottingham.ac.uk
Lead Organisation	Derby Teaching Hospitals NHS Foundation Trust Royal Derby Hospital Uttoxeter Road Derby DE22 3NE
Partner Organisations	Leeds Teaching Hospitals NHS Trust Bradford Teaching Hospitals NHS Foundation Trust Ashford and St Peters Hospital Frimley Park Hospital Surrey Pathology Services UK Renal Registry University of Bradford NHS England AKI Programme
Project managers	Melanie Johnson, Melanie.Johnson@yhahsn.nhs.uk Natalie Jackson, Natalie.Jackson@yhahsn.nhs.uk Carol Jones, Carol.AJones@asph.nhs.uk Julie Slevin, Julie.Slevin@renalregistry.nhs.uk
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Project summary

Title	Tackling acute kidney injury - a multi-centre quality improvement project
Protocol version and date	V5.1 October 2016
Objectives	To upscale an effective package of interventions for Acute Kidney Injury (AKI) and to measure the impact of its introduction across several partner organisations (across two regional networks) representing the range of UK hospitals.
Methodology	Quality improvement project with stepped wedge design for introduction of interventions. The package of interventions will be introduced sequentially across each network, one centre per three month period.
Project duration	30 months (including 6 month set up period)
Number of patients	Not defined – all patients sustaining AKI during the project lifespan will be included
Inclusion criteria	All hospitalised patients sustaining AKI in any of the partner organisations during the evaluation period of the project
Statistical methodology and analysis	We propose to evaluate the project on several different levels: *Patient outcomes:* Primary and secondary patient outcomes over each three month time period will be analysed, including effects for centre, time period and treatment variation between centres. A time series comparison between pre and post intervention periods will be made. Primary outcomes: 30 day mortality in patients with AKI Secondary outcomes: Incidence of hospital acquired AKI (h-AKI) Incidence of AKI progression Incidence of separate AKI stages Hospital length of stay (LoS) in patients with AKI Number of critical care bed days for patients with AKI Proportion of AKI patients with renal recovery by hospital discharge *Standards of care* Baseline and serial post-intervention audits (at each of the stepped wedges) of defined metrics of basic standards of care for patients who have sustained AKI. *Qualitative evaluation of the intervention package* Qualitative data about the utility and practicality of interventions will be collected, and will incorporate lessons learnt during the implementation process.

1 Introduction

This is a service improvement project, which includes an extensive measurement component to allow assessment of the efficacy of the interventions. We have aligned the proposal to the NHS England AKI programme to promote ongoing sustainability beyond the life of this proposal, but also to provide a project template that is transferrable and can be used in other AKI quality improvement projects. Data collection and analysis will be established via data streams to the UK Renal Registry and University of Bristol within existing approvals from the Health Research Authority (previously National Information Governance Board).

1.1 Background

Acute Kidney Injury (AKI) is a sudden reduction in kidney function. It is common, harmful and often preventable, thus representing a major patient safety challenge for the NHS [1]. AKI occurs in as many as 10-15% of hospital admissions [2], usually in conjunction with other acute illnesses. Elderly patients and those with chronic conditions such as heart failure, diabetes and chronic kidney disease (CKD) are most vulnerable [3]. The presence of AKI dramatically increases severity of patients' illness. Mortality rates of hospitalised patients with AKI are as high as 20-33% [4], whilst these patients are subject to longer, more complex hospital stays [5]. It is increasingly recognised that AKI also contributes to long term effects, in particular the development or progression of CKD [6].

As well as the adverse effects of AKI itself, there are many reports (in particular the 2009 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) Report) demonstrating that a significant component of the harm associated with AKI arises from poor standards of care [7]. It is also clear that only a minority of patients are cared for by nephrologists and AKI occurs regularly across all acute specialties. A major problem identified in the NCEPOD report were delays in diagnosis or even failure to recognise the presence of AKI, which often has a silent clinical course. Concurrently, it was demonstrated that early intervention focussed on basic elements of care can significantly improve the outcome of AKI [8]. It is therefore imperative that robust and scalable interventions are deployed to target these deficiencies.

2 Objectives

We propose to upscale an effective package of interventions for Acute Kidney Injury (AKI) and to measure the impact of their introduction across several partner organisations representing the range of UK hospitals. The aim is to improve the delivery of healthcare to patients with AKI that in turn will translate into better outcomes. We will assess the efficacy and the process of implementing the intervention on several levels:

1. *Impact on patient outcomes*
   A series of patient outcomes will be compared before and after introduction of the interventional package within a stepped wedge study design.
2. *Impact on quality of care delivered*
   Clinical audit of a series of defined metrics of basic care for patients who have sustained AKI
3. *Qualitative assessment of change process*
   Qualitative data from health care professionals (including members of the project team) will be used to evaluate practicality, acceptability and utility of interventions, whilst shared learning will allow ongoing tailoring of both the interventions and change methodology employed during implementation.

3 Project design

3.1 General design

This is a multi-centre quality improvement project using a stepped wedge design to sequentially introduce a package of interventions that has been trialled and shown to be successful at improving basic care and outcomes in patients who have sustained AKI in a single centre [9]. The interventions will comprise:

- An electronic AKI detection system based on biochemistry results and situated within pathology laboratory software, aimed at improving early recognition of AKI on a hospital-wide basis (section 5.1)
- An education programme to raise awareness and knowledge levels in all major medical and surgical specialities and across the range of health care workers (section 5.2)
- An AKI care bundle aimed at systematic improvements in the delivery of basic components of AKI care (section 5.3)

All patients sustaining AKI in the partner centres will be included; data collection will encompass a baseline measurement period before any change is instituted that will be compared with measurements after introduction of the package of interventions. Data collection will occur at each three month period of the stepped-wedge design in each partner organisation to provide additional methodological rigour over simple time-series comparisons. Baseline variation in current practice and differences in hospital characteristics (context) will be carefully recorded at project outset to allow subsequent assessment as to whether these differences impact on efficacy of interventions. Data collection and analysis will occur via links to the UK Renal Registry and University of Bristol, who will also provide expertise in change methodology and statistical support. NHS England will also provide partnership, and by aligning the proposal to the NHS England AKI programme board, we can demonstrate a realistic model to sustain change beyond the life of the proposal as well as a mechanism for wider scale adoption.

3.1.1 Change methodology

In addition to employing tried and tested interventions, their introduction will be supported by a structured approach to change management. This will be developed across each network of partner organisations (Yorkshire and Surrey) with arrangements for joint learning put in place. The detail of this will be tailored to each participating partner organisation but will consist of the following:

1. Planning stage, during which the following will be determined: profile of change characteristics, organisational attributes/characteristics profile, change management strategy, structure of local project teams, high level Trust engagement. There will also be a single learning event with representation from all partner organisations to refine the existing package of interventions. Pre-existing work from lead and partner organisations will be shared and discussed. From this, ideas will be shared and local versions of the most successful approaches to the interventions will be developed.
2. During the planning stage, the governance structure for the project will be settled, along with clear roles and responsibilities for key project team members.
3. Implementing change, of which there will be two main aspects:
    a. A peer-assist and peer-review programme. Centres at the start of implementation period will host a meeting during which their plans for implementating the interventions will be presented to team members from centres with experience (either the lead centre or centres ahead in the stepped wedge). With a challenge and confirm process, the following will be reviewed to maximise learning from prior experience (both explicit and tacit): where are you going to start; what formal/informal meeting structures exist to support the programme; measures intended; resources available and how they will be deployed; change methodology and expertise to support it; education plans; technology plans to support the project; how staff will be engaged; scope; timelines; risks how monitored
    At the end of implementation, a peer-review event will be held to include members from all centres, but in particular the next centre to implement in the stepped wedge. This will capture learning: What were our plans; What actually happened; What worked; What did we

have to change; What would we have done differently; What are they key learning points to share with the next organisation.

b. Measurement for improvement. Use of run charts or statistical process control charts (SPC) to monitor frequently progress with delivery/uptake of interventions, particularly around introduction of the care bundle. This measurement is separate from the other aspects of evaluation.

4. In addition, other key components will be: communication plan, senior engagement and buy-in.
5. Reinforcement to sustain change e.g. post-intervention audit to look at uptake, corrective action plans, individual and group recognition approaches, success celebrations, end of project review

Rather than adopting a reactive response to resistance to AKI improvement measures, the aim is to engage and empower clinicians caring for patients with AKI. We aim to demonstrate the clinical need, instil a desire to participate and support the changes as well as making the necessary knowledge available. Ease of use of interventions will be an over-riding principle and the change management process will be integrated from the beginning of the project, being a major focus of the six month set up period.

3.2 Primary endpoints

Patient outcome measures are taken as the primary end points for this project. Comparisons will be within-cluster (pre- versus post-intervention) and between-cluster to estimate the treatment effect. This approach is necessary to avoid confounding the treatment effect with changes over time comparing baseline and post-intervention time periods. The primary outcome measures are defined as:

1. 30 day mortality rate in patients with AKI

3.3 Secondary endpoints

Secondary outcome measures are separated into three groups. Comparisons will be within-cluster (pre- versus post-intervention) and between-cluster to estimate the treatment effect for patient outcome and clinical audit measures.

Patient outcome measures:

1. Incidence of hospital acquired AKI (h-AKI)
2. Incidence of AKI progression (defined as AKI that increases by at least one stage from AKI stage at time of first detection)
3. Incidence of individual AKI stages (stage 1, stage 2 and stage 3)
4. Length of hospital stay of patients with AKI
5. Number of critical care bed days used by patients with AKI
6. Proportion of patients with AKI who achieve complete renal recovery by hospital discharge. Renal recovery will be defined as serum creatinine returning to a value less than 27µmol/l above baseline creatinine value.

Measures of basic care:

Clinical audit will be completed in each centre to assess the proportion of patients with AKI who receive a series of metrics of basic care.

Qualitative data:

Qualitative data about the utility and practicality of interventions will be collected from health care workers involved in the provision of care to patients with AKI and from project team members. Specific record of facilitators and barriers to implementation would be made, alongside successful solutions to aid subsequent dissemination. These data will be collected at each partner organisation in the following ways: Face to Face interviews or Focus groups, and SurveyMonkey style questionnaires. Depending on local resources, we will explore the possibility of using TurningPoint software to collect data before and after teaching sessions. Results will be complied and compared between partner organisations.

4 Methods

4.1 Subjects

All patients aged ≥18 years who sustain AKI at the participating centres during the project lifespan will be included. The incidence of AKI will be expressed per number of hospital admissions during each time period. For the purposes of this project, patients will defined as having AKI if they have an inpatient blood test that triggers an AKI Warning Stage test result, using the NHS England AKI detection algorithm (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf). Hospital acquired AKI (h-AKI) will be defined as AKI that occurs >24hrs after hospital admission. Patients on long term dialysis will be excluded.

4.2 Data collection

All data used to assess the effectiveness of this project will be collected as part of routine clinical care. These data will be collected from electronic or paper hospital records without any additional patient interactions outside of that of routine clinical care.

Patient outcome data:
The following data points will be collected by setting up an IT report linking hospital outcome stay to electronic AKI detection results. It will also be acceptable to send separate files to the UKRR (for biochemical data and for hospital stay data) providing they both contain unique identifiers to allow subsequent linkage and removal of duplicates by the UKRR. A data specification will be issued to allow standardisation of data fields).
Data collection will need to occur when the results are suppressed (not visible to end-users during baseline periods) and when live in clinical practice (implementation periods). A report will be generated to cover each three month data collection period (as per figure below, section 4.3). Data collection will continue until each centre has completed two 3-month periods after the implementation phase. The report will include every patient aged 18 or over who has a hospital admission lasting ≥24hrs and with one or more AKI warning stage results generated from an inpatient serum creatinine concentration measurement. Depending on technical capabilities, ESRF patients will either be excluded based on dialysis clinical codes/unique monthly dialysis blood sets/location of blood samples (dialysis/renal unit).
Data set will include:

- Patient demographics: age at time of hospital admission, sex (male=1, female =0), ethnic group name/code
- NHS number (numerical field)/local identifier (text field)
- Date of admission (date field)
- Primary speciality (text field)
- Charlson co-morbidity score (numeric score) and constituent chronic disease binary scoring (1=present, 0=absent)*
- AKI data: initial AKI warning stage (numerical field limited to 1,2 or 3), highest AKI warning stage (numerical field limited to 1,2 or 3), time between admission and first AKI Warning stage result (numerical field, in hours), final inpatient creatinine result to assess recovery (numerical field, micromol/l)
- Hospital length of stay (numerical field, in days)
- ICU admission (1=admitted to ICU during hospital stay, 0=no ICU admission) and ICU admission length of stay (numerical field in days)
- In hospital mortality (numerical field, 1=died in hospital 0=survived to discharge)
- 30 day mortality (numerical field, 1=died within 30days of first AKI warning stage result 0=survived to >30days)
- Date of death (date field)

- In addition, for each three month period, the total number of hospital admissions will need to be returned (= elective and non-elective admissions, excluding day case contacts and patient discharged directly from ED).

[*] *Acute myocardial infarction, cerebrovascular accident, congestive heart failure, Connective tissue disorder, Dementia, Diabetes, Liver disease, Peptic ulcer disease, Peripheral vascular disease, Pulmonary disease, Cancer, Diabetes complications, Paraplegia, Renal disease, Metastatic disease, Severe liver disease, HIV*

UKRR data submission:

AKI warning stage data and serum creatinine concentration data will be submitted to the UKRR in line with the national guidance as per the following:

Audit of basic standards of care:

Sequential patients with AKI will be selected from designated audit periods, to include an equal number of patients with AKI stage 1, 2 and 3; AKI stage will be defined as maximum AKI stage during stay. Audit periods will consist of the final calendar month of each three month study period (1st baseline audit period May 2015). A list of all patients with AKI during these periods will be produced and used locally to select 30 patients at each centre (10 sequential cases for each AKI stage). Patients will be preferentially selected from the clinical areas in which the interventions are planned to or have been deployed with follow up audits in a similar hospital location.

Patients on a palliative care pathway will be exluded as will patients with End Stage Renal Failure on dialysis (NB patients with end stage renal failure with a renal transplant WILL be included). Audits will be carried out at baseline and then at each block of the stepped wedge period (total seven cycles per organisation, see figure below, section 4.3).

The following data points will be collected:

- Centre code
- Audit period (number field)
- Patient age (years), sex (male=1, female =0) plus other demographics as follows: ethnicity (as per NHS defn), NHS number, date of birth
- Date of admission (date field)
- Route of hospital admission (text field, limited list)
- First AKI stage during admission (number field limited to 1,2 or 3)
- Date of first AKI result (date field)
- Highest AKI stage during admission (number field limited to 1,2 or 3)
- Date of highest AKI result (date field)
- Ward descriptor of patient at time of AKI (text field, limited list)
- Duration of AKI
    a. Definition: number of days until serum creatinine returns to within 27micromol of baseline level for that individual
    b. Response options: 1 (=1-2days), 2 (=2-4days), 3 (= >4days), 99 (=not possible to define duration, e,g, creatinine not repeated, patient discharged prior to AKI resolution)
- Was AKI recognised?
    a. Definition: AKI recorded in hospital notes at any point during admission including discharge summary, use of AKI care bundle, investigation requested specifically for AKI
    b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)
- Was cause of AKI documented?
    a. Definition: cause of AKI recorded in hospital notes at any point during admission including discharge summary
    b. Response options: 1 (=yes), 0 (=no)

- If cause of AKI documented, enter all contributing factors as documented in hospital notes (text field)
- Was AKI care bundle used?
    a. Definition: AKI care bundle incorporated into patient record
    b. Response options: 0 (=no), 1 (=yes started within <6hrs), 2 (=yes started between 6-12hrs), 3 (=yes started between 12-24hrs), 4 (yes started between 24-48hrs), 5 (=yes started >48hrs), 6 (=yes but timing not known)
- Was AKI care bundle completed?
    a. DefinItion: All fields of AKI care bundle completed/signed for – this is an 'all or none' assessment
    b. Response options: 1 (=yes, 100% complete), 0 (=no, partially completed), 99(=care bundle not utilised)
- Did the patient receive a fluid balance assessment?
    a. Definition: any one of: patient examination incorporating assessment of volume status (including euvolaemia), clinical impression that includes reference to volume status, treatment plan includes correction of over- or under- hydration
    b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)
- Did the patient receive urinalysis at time of or following AKI?
    a. Definition: urinalysis results recorded in medical or nursing record
    b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known), 99(=not possible due to anuria).
    Urinary ACR/PCR is not equivalent and should not be counted as an acceptable alternative
- Proportion of patients with AKI who were taking relevant medications at time of AKI*
    a. Response options: 1 (=yes), 0 (=no) for each of the following:
    b. *Relevent medications: ACE inhibitor, ARB, MRA (e.g. spironolactone), NSAIDs ,diuretics in setting of dehydration, aminoglycosides, trimethoprim
- Proportion of patients with AKI who have had medication review
    a. Definition: treatment plan includes cessation of relevant medication*, treatment plan includes avoidance of relevant medication, relevant medications stopped within 24hrs of first AKI warning stage result, documented pharmacy review
    b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)
- Proportion of patients with AKI stage 2 or 3 who receive renal imaging
    a. Definition: renal ultrasound/CT/MRI imaging following onset of AKI
    b. Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) 99(=not appropriate – AKI stage 1 or senior clinician decision)
    c. If recording 99, state reason for coding as such (text field)
- Proportion of patients with AKI stage 3 who are discussed, referred to or seen by nephrology/ICU
    a. Definition: medical record contains documentation of telephone discussion with nephrology/ICU SpR or more senior, nephrology/ICU review or transfer to nephrology ward/ICU
    b. Response options: 1(=yes, discussion with nephrology), 2(=yes, referral to nephrology), 3(yes, discussion with ICU/outreach), 4(referral to ICU/outreach), 5(transfer to more specialist area; includes renal ward, high dependency or ICU), 0(=no), 99(=not appropriate – AKI stage 1 or senior clinician decision)
- In hospital mortality
    a. Definition: death during index hospital admission
    b. Response options: 1(=died during admission), 0(=survived to hospital discharge)

The audit will also include a process measure of care bundle usage and compliance. As well as a measure of implementation, this will also be used as a tool to promote ongoing usage of the care bundle. This will happen as part of the three monthly audit cycle of basic care, and will be the responsibility of the clinicians in each centre.

Other process measures:

- Number and type of educational interactions delivered at each site during each three month data collection period.
- Number of hits on local AKI guideline webpage in each three month data collection period. This will be used as a surrogate measure of AKI awareness in the organisation.

Qualitative data collection:

This will comprise of the following:

- Baseline questionnaire to be completed by each partner organisation prior to and during the design event to document context of their organisation and prior AKI work
- Recording implementation and validation of the AKI detection algorithm using the NHS England test script; this will evidence that each site is able to detect AKI and measure it in the same way. This will occur once at point of installation, supervised by lead biochemist in each organisation.
- Questionnaire/interview to be carried out with key personnel during implementation stepped wedge (therefore five in total)
- Depending on ethics approvals, we will explore widening this process to include frontline clinicians outside of the project team
- Review of transcripts/minutes of monthly project team teleconferences/meetings
- Collation of structured feedback from teaching sessions and on other educational materials (e.g. website, guidelines etc) and their interpretation within local context
- End of project interviews with project team members to record lessons for wider dissemination
- Results will be reviewed by participants to confirm and challenge (e.g. 'is this your experience…')

The focus of the analysis will be to identify patterns, themes, insights and understanding that will be organised into categories to aid presentation.

4.3 Flow diagram

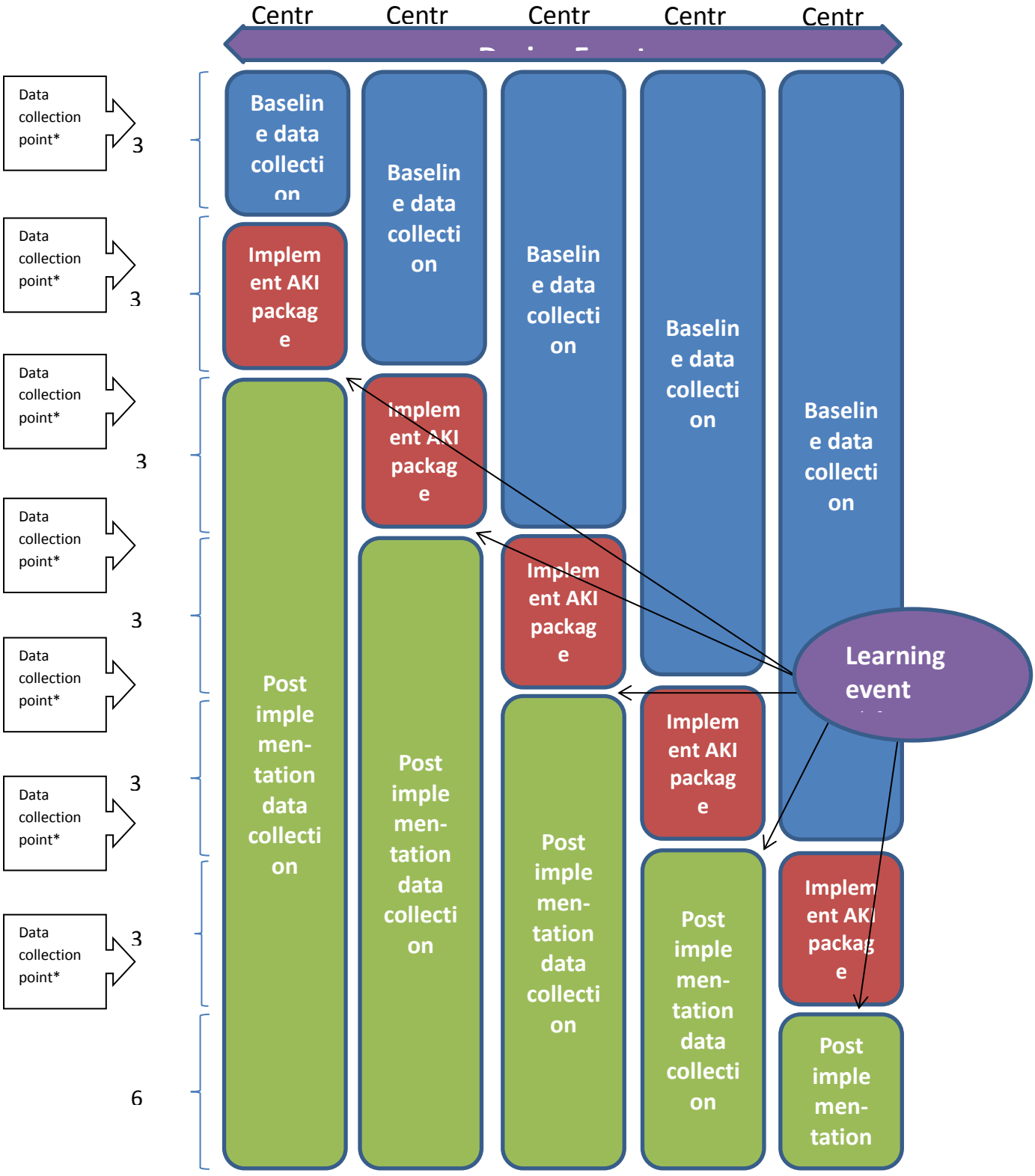

*Figure 1. Flow diagram showing step wedge design for implementation. *Data collection at each organisation will occur on a three monthly recurrenct cycle including baseline (1-5 times depending on position in stepped wedge), implementation (1 time per centre) and post-implementation (1-5 times). At each timepoint, data will be collected on: three monthly AKI incidence and outcomes (pt outcome data), process (audit of care bundle usage and basic standards of care, and number/type of education sessions delivered)*

5 Project procedures

The intervention package will be based on that implemented successfully at the lead centre. During the project planning stage, all centres will meet to share current experiences, review existing materials and refine these to maximise success in each partner organisation. Within this, there will be an ambition to standardise as much as possible. Variation in each of the interventions will be carefully documented throughout the life of the proposal.

5.1 Electronic AKI detection

Fully automated electronic AKI detection will be installed in the pathology Laboratory Information Management System (LIMS) at each participating centre. This algorithm will conform to the NHS England algorithm for the Early Detection of AKI (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf) and ensure compliance with the category 3 (directive) patient safety alert issued by NHS England in July 2014 (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki.pdf). This algorithm will generate a pathology test result (called AKI Warning Stage) for each creatinine result that is consistent with a diagnosis of AKI. This test result will be sent to each hospital's results reporting system or patient management system as for any other biochemical test result, and in this way be communicated to the clinicians caring for that patient. The warning score will be accompanied by a text string giving advice to the clinician.
Local variation in enhancements to alerting process will be explored depending on capability (e.g. linkage to electronic prescribing or other more interactive alerting processes.). Each centre will decide locally as to whether AKI results will be telephoned to clinical areas, and at which stage of AKI this will occur.

5.2 AKI guidelines

Intranet guidelines for the diagnosis, management and referral of AKI will support the introduction of electronic detection at each centre. The number of hits on the webpage will be recorded (if possible) as one measure of AKI awareness. A sample guideline (that can be locally adapted) is included as an appendix.

5.3 Education package

Specific education programmes will be deployed as part of the intervention. This will have several components, including face to face teaching (both small and large groups) and e-learning. The programme will encompass the major acute medical and surgical specialities, all grades of clinician and other members of the health care team that provide care to patients with AKI. The number, type and audience of teaching sessions delivered will be recorded across each partner centre. Education materials already available in participating units will be reviewed and shared during the project set up period (e.g. e-learning package that be viewed at http://www.uhl-library.nhs.uk/aki/). Sample education materials are included as appendices.

5.4 Care bundle

An AKI care bundle will be introduced at each centre alongside the detection and education elements of the intervention. The care bundle in use in the lead centre will be shared and then adapted for use in each partner organisation. The care bundles will be configured locally but will be based upon the following principles:

- Structured way of improving the care of patients
- Set of small, straightforward, evidence-based practices – generally three to five in total
- Occur at the same timepoint and in the same location
- Have to occur in totality (i.e. completing four out of five actions is non-compliant): compliance will be scored as all or nothing
- Clear accountability to 'who owns it' and 'who delivers it'
- Use of 'measurement for improvement' approach to support introduction and ongoing usage

6 Statistical plan

6.1 Sample size estimation

Sample size calculations were performed by UK Renal Registry. Annual number of admissions for each institution were taken from HSCIC (total admissions across all partner organisations 434,000pa). A conservative assumption of AKI incidence of 2.5% of admissions and a mortality rate of 27.5% were made; in this setting a stepped wedge design with three month adoption periods would give >80% power to detect a relative reduction of 20% in 30d mortality. This is both clinically relevant (equating to 597 fewer deaths each year) and plausible.

6.2 Statistical methods

A full statistical analysis plan will be developed as a separate document.

7 Data handling and Record Keeping

7.1 Confidentiality

Information about patients will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Calldicott Guardian, individual Trusts' IM&T Policy and the Health Research Authority. All audit data and hospital level patient outcome data will be stored on Trust password-protected computer/servers. Data transfer to the UKRR will occur within the UKRR's comprehensive governance framework that is already in place, and will contain only those specific data items that have given approvals by the HRA. Patients will not be identifiable from any reports or publications that arise from this project.

7.2 Source documents

Source documents will include:

- Electronic hospital admission data
- Hospital notes
- Laboratory reports and electronic reports that are generated using AKI warning score
- Paper copies of audit forms
- Run charts/SPC charts as appropriate

8 Ethical considerations

This project uses interventions consistent with minimum standards of care as per the NHS England AKI programme workstreams; Derbyshire Research Ethics Committee has designated this proposal as quality improvement and waived the requirement for formal ethical approval and individual patient consent. Transfer and collation of patient data by the UK Renal Registry (UKRR) is approved by the Health Research Authority under section 251 of the NHS Act 2006. Ethical approval for the qualitative evaluation of staff will be sought from the University of Bradford ethical committee.

9 Financial considerations

Funding will be provided by the Health Foundation (Scaling Up Improvement call).

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Statistical analysis plan for Tackling AKI Stepped Wedge Cluster Randomised Controlled Trial

List of collaborators

Nick Selby

Fergus Caskey

Anna Casula

Erik Lenguerrand

Shona Methven

Margaret May

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List of abbreviation:

AKI	Acute kidney injury
AT	As treated
CKD	Chronic kidney disease
CRT	Cluster randomised trial
HSCIC	Health and social care information centre
ICC	Intra-cluster correlation
ICU	Intensive care unit
ITT	Intention to treat
PAS	Patient administration systems
PP	Per protocol
RCT	Randomised control trial
RRT	Renal replacement therapy
SAP	Statistical analysis plan
SWCRT	Stepped-wedge cluster randomised trial
UKRR	United Kingdom Renal Registry

BACKGROUND

Acute Kidney Injury (AKI) is a sudden reduction in kidney function which is observed quite commonly during hospital stay, occurring in as many as 10-15% of hospital admissions [Wang et al., 2012]. It is harmful, and hospitalised patients with AKI have been shown to have longer, more complex hospital stays [Kerr at al., 2014], high hospital mortality rates [Selby et al., 2012] and higher risk of progression of CKD [Chawla et al., 2014].

The presence of AKI is also often recognised late or not at all, as it can have a silent clinical course and can present across many acute specialties so that not many patients developing AKI are seen by nephrologists.

It has been shown that a significant component of the harm associated with AKI arises from poor standards of care [NCEPOD report, 2009] and that early intervention focussed on basic elements of care can significantly improve the outcome of AKI [Balasubramanian et al., 2011]. It is therefore imperative that robust and scalable interventions are deployed to target these deficiencies.

While many patients are hospitalised with AKI already in progress (community acquired AKI), in many cases AKI develops during the hospital stay [hospital acquired AKI (h-AKI)].

This trial aims to deliver, across a range of UK hospitals, a package of interventions for Acute Kidney Injury (AKI) aimed to improve recognition and quality of care for AKI, and to assess how this translates into better outcomes in AKI patients and if this intervention can reduce the incidence of h-AKI (detailed protocol available on request).

For practical reasons this service can only be applied at the level of the population covered by the hospital and not on a subset of random patients within a hospital. Also the intervention is assumed to have a positive effect on AKI management/outcomes. For these reasons the study has been set up as a stepped-wedge cluster randomised trial (SWCRT), with the intervention applied at a cluster level and applied to all participating units by the end of the study. Such an approach overcomes any ethical problem of withholding a treatment considered likely to be effective, as the entire population recruited will receive the treatment by the end of the study. This approach also allows for differentiation between the effect of the intervention and potential independent unknown time-related factors.

There are no reporting guidelines specific to SWCRTs, so this Statistical Analysis Plan (SAP) is written to be consistent with the extension to cluster randomised trials of the CONSORT 2010 document [Campbell et al., 2012] and further suggestions recently published for SWCRT [Hemming et al, 2015]. This statistical analysis plan will guide the Trial Statistician during the statistical analysis of all quantitative outcomes in order to answer the objectives of the study.

STUDY DESIGN

A Stepped Wedge Cluster Randomised Trial approach will be taken. This means that the intervention will be delivered in sequential steps to one or more units of randomisation per time-period and

delivered to all the units of randomisation by the end of the study. This study has recruited 5 hospitals and is planned to take two years, between December 2014 and November 2016, with 2 initial control periods for all 5 hospitals, followed by 5 steps of randomisation (one hospital per step), and including a transition period (the first 'treatment period', when the treatment is expected not to have reached full efficacy on outcomes), for a total of 8 time-periods, each of 3 months in length (24 months in total – see Table-1, page.6).

THE INTERVENTION

The intervention (protocol, sections 3 and 5, available on request for details), has 3 parts:

- An AKI electronic detection system within pathology laboratory software
- An educational program to raise awareness and knowledge of AKI in care workers at hospital
- An AKI care bundle

The AKI electronic detection system has already been mandated at a national level (England only), with the plan to start nationwide from April 2015. The 5 hospital recruited for this SWCRT have been exempted from the initiative for the time being, so they would be able to wait to implement the intervention at their assigned time of randomisation, while having the electronic detection system in place since the end of 2014, but silent (as to measure the incidence of AKI during the baseline periods, with no active intervention).

OUTCOMES MEASURES

The outcomes of this study will be measured for all adult patients hospitalised overnight in the 5 participating hospitals, and identified as having an episode of AKI while in hospital by the pathology laboratory detection system (with results suppressed, non-visible to end-users, during control periods). The outcomes will be measured for the entire length of the study-period (1st Dec 2014 to 30th Nov 2016) for all of the AKI events, so multiple entries per patient are possible.

Primary outcome

- Thirty-day mortality after an episode of AKI. These are patient level data, binary outcome (0=patient alive 30 days after the AKI episode; 1=patient dead 30days after the AKI episode, logistic analysis).

Secondary outcomes

- 1. Incidence of h-AKI (aggregate data, counts, number of h-AKI cases, defined as AKI developed after >24hrs in hospital, with the denominator at risk being the total overnight hospitalisation episodes, Poisson analysis, standardised).

- 2. Incidence of AKI progression (defined as AKI that increases by at least one stage of AKI from AKI-stage at time of first detection) during hospitalisation. These are patient level data, binary outcome for each episode of AKI (0=did not progress during hospitalisation; 1=progressed during hospitalisation, logistic analysis).
  As we will not be able to determine for all patients diagnosed with level-3 AKI if they progress to need of acute dialysis during hospitalisation, we will perform this analysis to the cohort of AKI level-1 and level-2 episodes only.
- 3. Incidence of individual AKI stages (stage 1, stage 2 and stage 3). These are aggregate data, counts, to analyse as secondary outcome n-1.
- 4. Length of hospital stay of patients with AKI (patient level data, counts in days, potentially to analyse using Poisson model, depending on the distribution of this outcome)
- 5. Number of critical care bed days used by patients with AKI (patient level data, counts of days in ICU for each patients, possibly to analyse using Poisson or negative binomial model zero inflated, depending on distribution, as many counts of zeros are expected.
- 6. Achievement of complete renal recovery by hospital discharge in AKI patients (with renal recovery defined as serum creatinine returning to a value less than 27μmol/l above baseline creatinine value). These are patient level data, binary outcome on all AKI patients (0=did not recover during hospitalisation; 1=recovered during hospitalisation, logistic analysis).

RANDOMISATION UNITS AND TIME-PERIODS

In this trial, the primary outcome will be measured for each episode of AKI detected in patients hospitalised overnight, while the intervention will be implemented at hospital level. Hence this is a cluster randomised trial, where the units of randomisation are the participating hospitals.
In this trial the intervention will be implemented in a total of 5 hospitals, with only one hospital being randomised each time at each step (with a total of 5 randomisation steps), with time periods of 3 months length.

This intervention is complex and would take some time to deliver it. While the electronic detection system has been set up in advance (with results kept suppressed at baseline) and can be activated immediately at start of intervention, teaching to staff will require some time as well as change in practice to be established. For these reasons we expect to observe no quantifiable effects on the outcomes of AKI patients at first after intervention, and hence we have planned to have a transition period. While data on primary and secondary outcomes will be collected for all periods of the study, data from the transition period for each hospital will be excluded from the analyses. As this trial has sufficient power, we have planned for the transition period to be of the same length as the unexposed/exposed time-periods (3 months).
In summary (see Table-1), we are planning to have, for each hospital, two or more control periods (unexposed to the intervention, coded as ‘0’), one transition period (the first period of intervention,

including the period of staff training, when exposure has started but no effect is expected because of need of a minimum length of time for the treatment to reach full efficacy, coded as 'T') and one or more exposure periods, when the intervention has already been delivered for ≥ 3 months (exposed to the intervention, coded as '1').
A patient with AKI will be a 'control patient', a 'transition-patient or a 'treated/exposed patient' depending on when and at which hospital the AKI episode occurs.

Table-1 Scheme of timeline of trial.

Block	Dec'14-Feb'15	Mar-May'15	Jun-Aug'15	Sep-Nov'15	Dec'15-Feb'16	Mar-May'16	Jun-Aug'16	Sep-Nov'16
A	0	0	**T**	1	1	1	1	1
B	0	0	1	**T**	1	1	1	1
C	0	0	1	1	**T**	1	1	1
D	0	0	1	1	1	**T**	1	1
E	0	0	1	1	1	1	**T**	1

0=control, T=transition, 1=exposed

To define if the hospital has started the intervention in the assigned time frame, as per-protocol (PP), we will consider the date of activation of the pathology laboratory detection system (with results made active, visible to end-users). While ideally we expect the hospital to activate the system in the first week of the transition period, and to fully train the staff within these 3 months, we will consider the hospital as having followed the protocol as long as the date of activation of the detection system falls within the 3-months transition period assigned.

This study is not a longitudinal study of patients, but a study on repeated cross sectional data on patients that developed AKI in the same hospital, where patients included for each of the time-periods in the same hospital are usually different. Some of the patients could present more than once during a time-period (being hospitalised overnight and with an episode of AKI twice during 3 months) or could present with AKI multiple times in the same hospital but in different time periods. Correlation within patient will be accounted for in the analyses of AKI episodes' outcomes if multiple episodes occur in a non-insignificant portion of patients.

This study can be viewed as a longitudinal study when considering aggregate data at the level of the hospital. The only aggregate-data outcomes that will be analysed are the incidence of h-AKI and the incidence of AKI separately by level of AKI, which will be repeated measurement at hospital level. The repeated nature of these measurements will be taken into account when investigating for changes in AKI incidence after intervention.

SAMPLE SIZE CALCULATION

The annual number of hospital admissions in the 5 institutions recruited was taken from HSCIC (total annual admissions of about 434,000). We used a conservative assumption of AKI incidence of 2.5% of admissions and 30-days mortality rate after AKI of 16% [Selby 2012], which corresponds to an average of AKI episodes per hospital per 3 months of about N=540. Power was set at 80%, alpha at 0.05 and a range of values for inter class correlation (ICC) between 0.01-0.2 was considered. For the sample size calculations we used a Stata program [Hemming and Girling, 2014], which can accommodate for the transition periods. This showed that with a trial study-time of two years (Dec'14 – Nov'16) using the 5 units, with one unit per randomisation step and with one transition period (as in table-1), we would be able to detect a decrease in mortality from 16% to 12.8%. This corresponds to a reduction of about 20% in 30-days mortality, which is both clinically relevant (equating to around 300 fewer deaths each year for the total of the 5 units) and plausible.

RECRUITMENT AND RANDOMISATION

- Eligibility of hospitals

Considering this trial was starting in parallel to the AKI national program (with the need to temporarily exempt the hospitals recruited) and the knowledge that the numbers of AKI episodes in hospitalised patients are fairly high, we planned to limit the recruitment to only 5 hospitals. For convenience the following 5 units were recruited, 2 from Surrey (Ashford and Frimley Park) and 3 from Yorkshire (Bradford, Leeds General and Leeds St. James).

- Eligibility of patients

Adult patients (>=18yrs) hospitalised overnight in the participating hospitals are eligible if they should present in hospital with AKI or develop an episode of h-AKI, during the study period. In particular, AKI will be identified by having an inpatient blood test that triggers an AKI warning stage result, using the NHS England AKI detection algorithm (http://www.england.nhs.uk/wp-content/uploads/2014/06/psa-aki-alg.pdf), both in the control/baseline periods (when results are suppressed, not visible to end-users) and implementation periods.
Patients that are identified as having AKI but were already on chronic dialysis are not eligible and will need to be excluded, while patients with a renal transplant are eligible.

The five hospitals were recruited and the randomisation took place on the 11th of May 2015. Randomisation was performed using SAS-9.3 (RANUNI function), to generate 5 random numbers. These were then allocated to the five hospitals (listed in alphabetical order, based on hospital name), and finally the hospitals were sorted based on their random numbers, from smallest to highest, giving the sequence of randomisation.

DATA SOURCE, COLLECTION AND VALIDATION

Data from hospitals

All data used for the analyses described in this document will be collected as part of routine clinical care, from electronic hospital records. Patient level data will be extracted from the hospitals' PAS for all patients flagged by the AKI electronic detection system. The data extracted will be sent to the UKRR. If data are sent in separate files, each file will need to contain unique patient identifiers to allow subsequent linkage and removal of duplicates by the UKRR.

Data set (see https://www.thinkkidneys.nhs.uk/wp-content/uploads/2014/12/AKI-Warning-Algorithm-Best-Practice-Guidance-final-publication-0112141.pdf for details) will include:

- Patient identifiers and demographics:
  NHS number or Local Patient Identifier
  Date of birth
  Gender (M/F/U)
  Ethnicity (name/code)
- Date of admission and date of discharge
- Primary specialty (text field)
- Charlson co-morbidity score (numeric score) and constituent chronic disease binary scoring (1=present, 0=absent)
- In hospital mortality (numerical field, 1=died in hospital 0=survived to discharge)
- 30 day mortality (numerical field, 1=died within 30days of first AKI warning stage result 0=survived to >30days)
- Date of death (date field)
- Length of hospital stay (numerical, in days)
- ICU admission (1=admitted to ICU during hospital stay, 0=no ICU admission) and ICU admission length of stay (numerical field in days)
- AKI data (see https://www.thinkkidneys.nhs.uk/wp-content/uploads/2015/01/Transmitting-AKI-Warning-Stage-Data-to-the-UKRR-final.pdf for detailed specification): initial AKI warning stage (numerical field limited to 1, 2 or 3), highest AKI warning stage (numerical field limited to 1, 2 or 3), time between admission and first AKI Warning stage result (numerical field, in hours), final inpatient creatinine result to assess recovery (numerical field, micromol/l).
- Data on population at risk: For each of the 3-months periods, the total number of hospital admissions in adult patients (>=18yrs old, elective and non-elective admissions, excluding day case contacts and patient discharged directly from ED) will be needed to estimate the population at risk to analyse incidence of AKI. If possible, hospitals will return a file containing the full list of those admissions, without any patients' identifier, but containing age (rounded to unit), gender and ethnicity of patients. This will allow the statistician to perform a standardised analysis of AKI incidence rates, without having to pre-specify to the hospitals the level of standardisation. If this is not possible, the total number of admission should be given,

preferentially by age-group (18-<25, 25-<30, 30-<35 and so on in 5-years age-bands), gender and ethnicity (South Asian, Black, Other (including mixed race and Chinese), White and Missing).

While the hospitals are responsible for identifying and excluding patients that were in day-care or were already receiving chronic dialysis, the data item 'time between admission and first AKI Warning stage result' will allow the analysts at the UKRR to distinguish episodes of community-acquired AKI and hospital-acquired AKI. Any hospital that should not be able to automatically apply the exclusion of those patients already on dialysis will need to provide the UKRR with necessary extra variables to identify these patients.

Hospitals will also need to let the UKRR know of any re-organisation of their laboratories during the study period, if this should occur. Such changes could cause an increase in the detected incidence of AKI, related to the cases of suspected-AKI. This trial does not analyse suspected-AKI (when an episode of AKI is suspected because of high values of creatinine but there are no baseline measurements). However, if links with new laboratories should occur during the study periods, and historical data are uploaded in the hospital lab-network, more baseline measurements could be available to the hospital and therefore the hospital would be able to appropriately flag more AKI episodes than previously, which could result in an apparent increase in incidence of AKI. If this should happen we will be able to investigate this as the AKI-dataset, providing the values of creatinine used in the e-alert, include a code of the lab that produced each specific data point. Also we expect to obtain from each hospital a measure of suspected-AKI for each time period. Using this information we could be able to adjust the analysis of incidence of AKI using a measure of incidence of suspected-AKI or alternatively we could exclude from the incidence analysis those AKI-episodes that were detected because of the new laboratory links. Best way to proceed will be decided once data are available, based on data completeness and reliability, if this event should occur.

Data collection from hospitals will occur every 3 months, to cover each 3month period. As the primary outcome is 30-day mortality, data for each period will be extracted with a minimum of 10 weeks delay (e.g. data for June-August 2015 will be extracted during the second half of Nov'15) or longer, depending on the capability of each hospital to update PAS.

Data from renal units

No data on acute or chronic RRT will be used in this analysis.

We would have preferred to include the need of acute dialysis or start of chronic dialysis during hospitalisation as a step of progression for AKI in the analysis of the secondary outcome n-2, but we were aware that information on acute dialysis would not have been complete, especially for those hospitals that do not have a renal unit within the hospital. As a consequence, we will not be using any information known to the UKRR on start of RRT in the analysis.

However, depending on completeness of patient identifiers such as NHS-number, the UKRR will perform a match of the patients with AKI with the RRT patients, available from the UKRR database. This will be done to validate the adherence to the exclusion criteria (exclude episodes of AKI from patient already on dialysis) applied by the hospitals before transferring the data to UKRR. The UKRR routinely collect data on RRT patients for all of UK, and by the summer of 2017 it should have the data on all RRT patients starting RRT up to Dec'16, which will cover the cohort of this study. Using the date of hospital admission and the date of RRT start in those patients matched, the analyst at UKRR will determine if any of the episodes of AKI included in the analysis occurred in dialysis patients, and exclude the appropriate episodes from the final analysis.

POTENTIAL PROBLEMS

- Missing data. Completeness of patients' demography from PAS is known to be high for age and gender, but we do expect missing data for the variable 'ethnicity'. The outcome variables (AKI-level and changes, length of hospital stay and use of critical care beds) are expected to be complete, as well as mortality. If the percentage of entries with some missing demography data is low and appears to be distributed at random (with mortality equally distributed between set of data with complete covariates and set of data with some missing covariates) and if the power of the analysis is not compromised, we will perform the analysis restricting the cohort to AKI episodes with complete data. However, if the completeness of the variable 'ethnicity' should be too low, we will exclude this variable from the adjustment in all analyses and use the dataset with complete age/gender/comorbidity score. Multiple imputation will not be attempted as we don't believe we have enough variables to perform a valid imputation.
- There is a risk that the time of implementation in some hospitals will slip. The impact of this will be explored in both a 'per protocol' and 'as-treated' secondary analysis.
- It is possible that a hospital will drop-out from the trial after being randomised (so no intervention at all). If this occurs, the impact will be explored in a per protocol analysis.

STATISTICAL ANALYSIS

Analyses of primary and secondary outcomes will be conducted at the UKRR in collaboration with the University of Bristol, using Stata MP12 and SAS 9.3.

Number of participants

We will present a table with number of total overnight hospitalisation episodes in adult patients, number of episodes of AKI (and numbers of patients with AKI episodes) and number of AKI episodes with complete set of variables, by hospital, per time-period (Table-2).

Table-2. Example of how numbers of AKI episodes and data completeness could be presented

Hospital		N total overnight Hospitalisations	N episodes of AKI (N patients)	N hospitalisation with AKI and complete covariates (% of tot AKI)
A	TP_1	20,000	500 (450)	480 (96%)
	TP_2			
	TP_3			
	TP_4			
	TP_5			
	TP_6			
	TP_7	21000	580 (540)	550 (95%)
	TP_8		etc.	
B	TP-1	16,000		
	TP-2	15,500		
	TP-3	16,500		
	TP-4			
	TP-5			
	etc.			

White=control; Orange=Transition; Yellow=exposed; 1 hospital per block, numbers for each time-period

TP=time period, 1=1stDec'14-28Feb'15, 2=1stMar-31may'15, and so on

Interim analysis and data quality

No interim analysis will be conducted on the primary and secondary outcomes. However data monitoring will be done to insure that the data collected by the hospitals via PAS are in the right format a first time by March 2016 from all of the 5 hospitals, and then again every 3 months for each of the hospitals.

We will also test the matching process of patients with AKI with the RRT patients in the UKRR database a first time in March 2016 and then again at the end of the study.

The last data collection should occur around Feb-Mar'17.

Descriptive statistics

The characteristics of patients with episodes of AKI by exposure (control versus intervention) and their outcomes will be presented for each hospital. We don't expect significant differences in the demographic of the population feeding to each hospital during the 2 years study-period, and therefore the number of people presenting with AKI and needing hospitalisation is not expected to change with the intervention (as the incidence is determined by the AKI-alert activation in both baseline and exposed periods). However we hope to observe a decrease in h-AKI with the intervention, as this will hopefully increase awareness of AKI and use of protocols that minimise risks of AKI development.

Therefore when comparing the unexposed versus exposed patients with AKI, differences could be expected, if incidence of h-AKI should be influenced by the intervention differentially in specific subgroups of the hospitalised population (e.g. if h-AKI preventable in the younger but not in the older, then the post-intervention AKI population will be older).
Also, each hospital covers different population-mix, and while each one will contribute both control and exposed AKI-patients, they will do so in different proportions, depending on when they are randomised to the intervention. This will contribute greatly to any difference in demography between the control and the exposed groups.
Whilst we do not intend to test for differences in demography between control and exposed groups for the full cohort, we will adjust the analyses for the covariates described because of the potential imbalance across hospitals and across steps.

We will present categorical variables as numbers and percentages. Continuous variables will be presented using mean and standard-deviation, or median and interquartile range, depending on their distribution (see Table-3).

Table-3

Hospital	Variable	Control	Exposed
A	N episodes (N patients) % male Ethnicity age-group comorbidity score % AKI levels (1-2-3) % h-AKI over total AKI (or incidence of h- AKI) N deaths by 30days Length hosp-stay (median-IQR) N Critical care (% >0) N recovered (%) N progressed (%)		
B etc	N % male Ethnicity age-group		

More detailed graphical representation of the primary outcome (30 day mortality) will be given (see Figure-1 for example). Summary results of secondary outcomes will also be presented in graphical or table format.

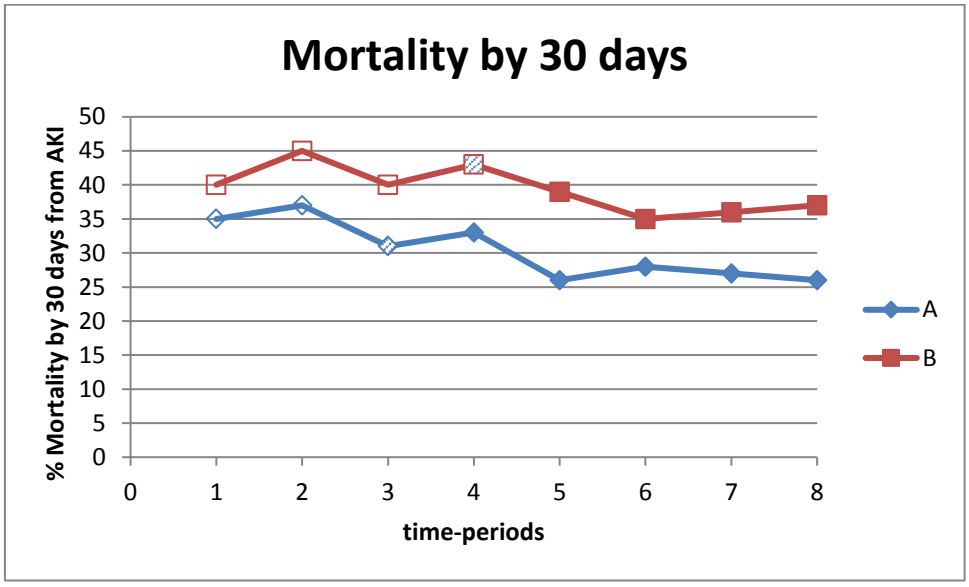

Figure-1. Example of graphical presentation of 30-days mortality data for hospitals A and B, where empty symbol=control, pattern symbol=transition, full symbol=exposed).

Analysis of primary outcome

The primary outcome (30 day mortality) is the only outcome that will be observed in a fixed time interval starting at date of admission rather than during the hospitalisation spell. While some hospitalisation spells will last one month or more, most will be shorter. As we have previously pointed out, multiple episodes (hospitalisations with AKI) in the same patient can occur. This is not a problem when the outcome is related exclusively to the hospitalisation spell (duration, ICU, recovery, progression). However in the analysis of 30 day mortality the presence of multiple episodes could create a problem, if the multiple episodes should occur within a month. For example a patient could be hospitalised with AKI for a week, return at home and re-hospitalised a second time after a week, and die in hospital after few days, in which case the patient will be present twice in the cohort, both times with an outcome of death within 30 days. For this reason, only in this analysis, we will exclude repeated AKI-episodes that occur within a month from the previous hospitalisation, whichever the outcome. A case like the one just described will appear only once in the dataset, while a patient that is hospitalised with AKI for a week, then is back at home for 4 weeks, and then re-hospitalised with AKI again will appear twice.

Analysis of 30-day mortality will be done using a mixed-effects logistic regression, as a patient level analysis, and accounting for correlations between episodes in the same hospital by including hospital in the model as a random effect. If a non-insignificant proportion of episodes of AKI should be multiple episodes in same patients, we will also account for the correlation between episodes in the same patient by fitting a second random effect for patient in the analysis. The primary outcome response

will be binary (patient died by 30days after AKI=1, patient still alive after 30days since AKI=0). Mortality is expected to decrease after the intervention.

The odds ratio estimate of the mortality risk for the treatment effect (intervention versus control) with 95% confidence interval will be presented (Model-1). Analysis will be adjusted by time-period (step) (Model-2) and individual patients' characteristics (Model-3) such as age at hospitalisation, gender, possibly ethnicity, and Charlson comorbidity score.

The impact of the intervention on outcomes could potentially change over time, as it could increase in time with increased experience of staff, but could also decrease after an initial improvement (as enthusiasm decrease/new staff not properly trained and so on) and therefore we aim to explore for possible interaction between time and treatment effect (Model-4).

The results from Model-3 will be considered the primary result, as the aim of this trial was to determine if any change after treatment in short-term mortality is related to the intervention and not to an independent calendar time trend, and since the primary outcome 'mortality' is highly correlated to age, the results adjusted by patient-demographic are believed to be the most appropriate.

Model building

Using the following notation:

- I clusters (i=1,2…5)
- M time points (j=1,2 … 7)
- N episodes (k=1, 2 …..N), sampled per cluster per time point (cross-sectional cohort)
- Treatment indicator (T_{ij}), equals 1 if intervention present at cluster I at time J, else it is 0.
- A fixed treatment effect (θ)
- Fixed time effect (γ_j) (one parameter if calendar time used as continuous variable, otherwise vector)
- Fixed effects [β] for patient-level demographics
- Patient-level adjustment variables [X_k]
- Random cluster effect (α_i)
- Residual noise (ε_{ijk})

We will start with a unadjusted Before/After analysis of the effect of intervention (ignoring time effect)

MODEL-1 $\text{Logit}(Y_{ik}) = \theta * T_i + \alpha_i + \varepsilon_{ik}$

Where Y_{ik} = probability of the episode to have response=1 (death by 30-days after AKI)

θ = log odds for the treatment variable (1=exposed, 0=control) in centre I

Then we'll build in the effect of time-period (step) to investigate if any potential treatment effect is related only to the treatment or also to an independent effect of calendar time.

MODEL-2 $\text{Logit}(Y_{ijk}) = \theta * T_{ij} + \gamma_j + \alpha_i + \varepsilon_{ijk}$

Where γ= log odds for the effect of Time (vector if effect not linear)
Calendar time could be a potential confounder as other factors/events (e.g. other changes in NHS practice) could influence the outcome measure in both control and exposed patients. As this effect could be anything from absent, or gradual (progressive slow trend) to abrupt, (near simultaneous adoption of a new practice that has an immediate full-strength effect), calendar time will be fitted in the model first as categorical and then as a linear variable, and appropriate fitting will be chosen.

Then adjustment for patient-level characteristics at time of AKI-episode will be included in the model

MODEL-3 $\text{Logit}(Y_{ijk}) = \theta * T_{ij} + \gamma_j + [\beta]X_{ijk} + \alpha_i + \varepsilon_{ijk}$

Where $[\beta]$ = log odds for matrix of X covariates for the episode K in centre I at time J

The covariates of adjustment used in this analysis are the following: age at hospitalisation (linear or divided by age-group as needed), gender, possibly ethnicity, and Charlson comorbidity score.

Further to this, time will also be fitted as time since exposure (time as treatment effect modifier), to examine how the impact of the intervention develops over time (how long does it take to see a full size effect of the intervention over the primary outcome and if the size of the effect is maintained over time)

MODEL-4 $\text{Logit}(Y_{ijk}) = \theta * T_{ij} + \gamma_j + [\beta]X_{ijk} + \omega Q_{ij} + \alpha_i + \varepsilon_{ijk}$

Where ω = log odds for the interaction between Time and Treatment (variable Q, analysed as numerical variable (0=any control period, 1=1st exposure step, 2=2nd exposure step, etc.) for centre I at time J. This will be fitted as continuous and categorical and the most appropriate fitting will be chosen.

The primary analysis will be performed on an intention to treat basis (ITT), with a unit considered to have followed the protocol if the e-alert system was activated within the 3months 'transition period' they were allocated to. As this is a complex intervention to roll out, some deviation from protocol is expected to occur. In this case also a per-protocol (PP) analysis and an as-treated (AT) analysis will be performed and all results will be presented.

For the PP analysis, we will exclude from the analysis the data collected during those time-periods where treatment did not coincide with that expected from the protocol (see table 4 for example).

Table-4: PP analysis data exclusion

Block	Dec'14-Feb'15	Mar-May'15	Jun-Aug'15	Sep-Nov'15	Dec'15-Feb'16	Mar-May'16	Jun-Aug'16	Sep-Nov'16
A-protocol	0	0	**T**	1	1	1	1	1
A-as done	0	0	0	0	**T**	1	1	1
A-data used	YES	YES	**NO**	**NO**	**NO**	YES	YES	YES

The as-treated analysis will include all cases of AKI as 'control' or 'treated' based on the treatment that patients had received at time of AKI episode, rather than the treatment they were assigned based on the allocation process. In this case 1st day of the month when e-alert was activated in each hospital will be considered the start of that hospital's transition period.

The report will include adherence to the timing of randomisation to intervention.

NOTE: If a logistic model should not run/iterate then we will use an equivalent mixed-effects linear regression analysis, approximating by using 0 and 1 as a continuous variable for the dichotomous variable of 30 days mortality (Hussey and Hughes, 2007).

Analysis of secondary outcomes

- The aggregate-data secondary outcomes 1 and 3 (incidence of h-AKI and incidence of AKI by level of AKI - expressed as number of patients developing AKI per hospitalised population), will be analysed using a Poisson regression, standardised by age and gender and, if possible, by ethnicity.

This will be a cluster-level Poisson analysis, with one measure per time-period per hospital, if unadjusted (or one measure per time-period per hospital per age-gender subgroup, if standardised).

MODEL $\text{Log}(Y_{ij}) = \log(\text{exposure}_{ij}) + \theta * T_{ij} + \gamma_j + \alpha_i$

Where Yij = count of AKI episodes in hospital I at time J

Exposure-ij=denominator, number of hospitalisations in hospital I at time J
θ = effect of the treatment variable (T=1 exposed, T=0 control) in centre I at time J
γ= effect of Time (vector if effect not linear)

(+ ωQij in the model if we want to investigate interaction between Time and Treatment)

- For secondary outcome n-2 (progression of AKI, binary outcome), we will use the same analysis as for the primary outcome (mixed-effect logistic regression), limited to the cohort of episodes classified as level-1 and level-2 AKI at time of first detection.
- The analysis of length of hospital stay (see outcome 4, page-5) in patients with AKI will be done with the model most appropriate to the distribution of this outcome. As these data are count data (days in hospital, integers >=1), Poisson analysis with episode-level data, adjusted for clustering at centre, is expected to be appropriate. However if the distribution should be approximate to normal or over-dispersion should be observed, mixed-effect linear regression or negative binomial models will be considered. The same model building sequence will be used as in the logistic analysis of the primary outcome.
- Number of critical care bed days (outcome 5, see page 5), will be analysed based on the distribution of the outcome. This is a count outcome, expected to be zero inflated, therefore a negative binomial analysis will be considered if over-dispersion is observed, or logistic regression if very little dispersion is observed for this outcome (0=No days in ICU, 1=one or more days in ICU).
- For secondary outcome n-6 (recovery of AKI, binary outcome, see page-5), we will use the same analysis as for the primary outcome (mixed-effect logistic regression). In this analysis, if patient should die during hospitalisation before recovery of function, the episode will be counted as a non-recovery, while if patient recovers renal function during hospital stay but then dies, the episode will still be considered as a recovery.

TIMELINE FOR ANALYSIS

	Dec 2014 - Nov 2015				Dec 2015 - Nov 2016				Dec 2016 - Nov 2017			
	D-F	M_M	J-A	S-N	D-F	M_M	J-A	S-N	D-F	M_M	J-A	S-N
Develop statistical analysis plan												
Randomise units to steps												
Baseline period-1												
Baseline period-2												
1st Transition												
2nd Transition												
3rd Transition												
4th Transition												
5th Transition												
Last period, all on treatment												
Provide 1st report on data												
Statistical analysis and write up												

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PATIENT INITIALS ☐☐☐ CENTRE CODE ☐☐☐

TACKLING AKI: AUDIT CASE REPORT FORM

AUDIT PERIOD (number from 1-7): ☐

HIGHEST AKI STAGE:

☐ 1
☐ 2
☐ 3

Date of highest AKI stage:

__ __ / __ __ / __ __ __ __
DD / MM / YYYY

Demographic Data

NHS Number: ☐☐☐ ☐☐☐ ☐☐☐☐

Date of Birth: __ __ / __ __ / __ __ __ __
(DD / MM / YYYY)

Ethnicity:

White:	White British ☐	White Irish ☐	White Other ☐	
Mixed race:	White & Black Caribbean ☐	White & Black African ☐	White & Asian ☐	Other mixed background ☐
Asian or Asian British:	Indian ☐	Bangladeshi ☐	Pakistani ☐	Other Asian background ☐
Black or Black British:	Caribbean ☐	African ☐	Black Other ☐	
Chinese or other ethnicity:	Chinese ☐	Other ☐		

Gender: ☐ Male ☐ Female

Admission Data

Date of hospital admission: __ __ / __ __ / __ __ __ __
(DD / MM / YYYY)

Route of hospital admission

Type:	Elective ☐	Non-elective ☐		
Source:	Via ED ☐	Direct to admissions unit ☐	Direct to ward ☐	Transfer from other hospital ☐

Ward descriptor at time of AKI onset

ED ☐	Medical admissions unit ☐	Surgical admissions unit ☐		Nephrology ward ☐
Medical ward ☐	Surgical ward ☐	HDU ☐	ICU ☐	Other ☐

PATIENT INITIALS ☐☐☐ CENTRE CODE ☐☐☐

AKI data				
Initial AKI stage:	☐ 1 ☐ 2 ☐ 3			
Date of initial AKI stage:	__ __ / __ __ / __ __ __ __ (DD / MM / YYYY)			
Duration of AKI	1-2 days ☐	2-4 days ☐	>4 days ☐	Not possible to determine ☐

Was AKI recognised during hospital admission?			
No ☐			
Yes:	Within 6hrs of AKI onset ☐	Within 6-12hrs of AKI onset ☐	Within 12-24hrs of AKI onset ☐
	Within 24-48hrs of AKI onset ☐	>48hrs of AKI onset ☐	Recognised but timing not known ☐

Was cause of AKI recorded? ☐ Yes ☐ No

If cause of AKI was recorded, enter causative factors <u>as recorded in hospital notes</u> *(leave blank if cause of AKI not documented)*

Patient outcome:
☐ Died during hospital admission
☐ Survived to hospital discharge
☐ Transferred to another hospital

PATIENT INITIALS ☐☐☐ CENTRE CODE ☐☐☐

Process of care data			
Was AKI care bundle used?			
No ☐			
Yes:	Within 6hrs of AKI onset ☐	Within 6-12hrs of AKI onset ☐	Within 12-24hrs of AKI onset ☐
	Within 24-48hrs of AKI onset ☐	>48hrs of AKI onset ☐	Yes but timing not known ☐
Was care bundle completed in full:	☐ Yes ☐ No ☐ Care bundle not utilised		

Did the patient receive a fluid balance assessment?			
No ☐			
Yes:	Within 6hrs of AKI onset ☐	Within 6-12hrs of AKI onset ☐	Within 12-24hrs of AKI onset ☐
	Within 24-48hrs of AKI onset ☐	>48hrs of AKI onset ☐	Yes but timing not known ☐

Did the patient receive urinalysis at the time of or following AKI?			
No:	Not done ☐		Anuric ☐
Yes:	Within 6hrs of AKI onset ☐	Within 6-12hrs of AKI onset ☐	Within 12-24hrs of AKI onset ☐
	Within 24-48hrs of AKI onset ☐	>48hrs of AKI onset ☐	Yes but timing not known ☐

Was the patient receiving any of the following medications at time of AKI?				
	ACE inhibitor ☐	Angiotensin receptor blocker ☐	NSAID ☐	MRA ☐ (e.g. spironolactone)
	Loop diuretic ☐	Thiazide diuretic ☐	Aminoglycoside ☐	Trimethoprim ☐

PATIENT INITIALS ☐☐☐ CENTRE CODE ☐☐☐

Did the patient receive a medication review at time of or after AKI?						
No ☐						
Yes:	Within 6hrs of AKI onset ☐		Within 6-12hrs of AKI onset ☐		Within 12-24hrs of AKI onset ☐	
	Within 24-48hrs of AKI onset ☐		>48hrs of AKI onset ☐		Yes but timing not known ☐	

FOR AKI STAGE 2 AND 3 ONLY: **Did the patient receive renal imaging?** Not answered, patient AKI stage 1 only ☐						
No:	Not done ☐		Not appropriate ☐			
Yes:	Within 6hrs of AKI onset ☐		Within 6-12hrs of AKI onset ☐		Within 12-24hrs of AKI onset ☐	
	Within 24-48hrs of AKI onset ☐		>48hrs of AKI onset ☐		Yes but timing not known ☐	

FOR AKI STAGE 3 ONLY: **Did the patient receive specialist input (renal/ICU)** Not answered, patient AKI stage 1 or 2 only ☐						
No:	Not done ☐		Not appropriate ☐			
Yes:	Discussed with nephrology ☐		Seen by nephrology ☐			
	Discussed with ICU/CCOT ☐		Seen by ICU/CCOT ☐		Transfer to specialist area ☐	

** CCOT = critical care outreach team*

Balancing measure						
Was patient catheterised as part of AKI care?						
No:	Not done ☐		Not possible (e.g. long term cathether) ☐			
Yes:	To relieve obstruction ☐		Yes, for any other reason including fluid balance monitoring ☐			

Completed by: _____
Name Signature Date

TACKLING AKI: AUDIT SUPPORT INFORMATION

CENTRE CODE	FRI: Frimley BRA: Bradford ASP: Ashford and St Peters LGI: Leeds General Infirmary LSJ: Leeds St James'
AUDIT PERIOD	Enter number corresponding to the audit period as below 1. May 2015 (baseline) 2. August 2015 3. November 2015 4. February 2016 5. May 2016 6. August 2016 7. November 2016 (post intervention at all sites)
HIGHEST AKI STAGE DURING HOSPITAL ADMISSION	Number field either 1,2 or 3 *(placed at top of the form as 10 cases from each stage required for each audit period)*
DATE OF HIGHEST AKI STAGE	Date field: DDMMYYYY
NHS NUMBER	10 digit number
DATE OF BIRTH	Date field: DDMMYYYY
ETHNICITY	As per NHS definitions
GENDER	Male or female (male=1, female =0)
DATE OF HOSPITAL ADMISSION	Date field: DDMMYYYY
ROUTE OF HOSPITAL ADMISSION	a) Elective (planned) admission =1 or Non-elective (emergency) admission =2 b) Admission source: route via which patient entered hospital. Emergency Department (=1), Direct to Admission Unit (=2, either medical or surgical), Direct to ward without passing through ED or MAU/SAU (=3), Transfer from other hospital (=4)

WARD DESCRIPTOR AT TIME OF AKI ONSET	ED (=1), MAU (=2), SAU (=3), Nephrology ward (=4), General medicine ward (=5), High dependency (level 2) unit (=6), Intensive care unit (=7), General surgical ward (=8) Other (=99)
INITIAL AKI STAGE	First AKI warning stage during hospital admission (as per NHS England AKI Warning Stage algorithm) i.e. AKI stage at onset of AKI. Number field either 1,2 or 3
DATE OF INITIAL AKI STAGE	Date field: DDMMYYYY
DURATION OF AKI	a) Definition: number of days until serum creatinine returns to within 27micromol of baseline level for that individual. For the purposes of this audit, baseline defined as most recent stable creatinine level prior to AKI. b) Response options: 1 (=1-2days), 2 (=2-4days), 3 (= >4days), 99 (=not possible to define duration, e,g, creatinine not repeated, patient discharged prior to AKI resolution)
WAS AKI RECOGNISED DURING HOSPITAL ADMISSION?	a) Definition: AKI recorded in hospital notes at any point during admission including discharge summary, use of AKI care bundle, investigation requested specifically for AKI b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)
WAS CAUSE OF AKI RECORDED?	a) Definition: cause of AKI recorded in hospital notes at any point during admission including discharge summary b) Response options: 1 (=yes), 0 (=no)
IF CAUSE OF AKI WAS RECORDED ENTER CAUSATIVE FACTORS	Enter as recorded in the hospital notes ONLY (text field)
DID PATIENT DIE DURING ADMISSION?	If patient died during index hospital admission: yes(=1), no(=0), transferred to another hospital (=2)
WAS AKI CARE BUNDLE USED?	a) Definition: AKI care bundle incorporated into patient record b) Response options: 0 (=no), 1 (=yes started within <6hrs), 2 (=yes started between 6-12hrs), 3 (=yes started between 12-24hrs), 4 (yes started between 24-48hrs), 5 (=yes started >48hrs), 6 (=yes but timing not known) If the audit period is occurring before your centre has implemented the care bundle answer no for all cases.

WAS THE AKI CARE BUNDLE COMPLETED?	a) Definition: All fields of AKI care bundle completed/signed for – this is an 'all or none' assessment b) Response options: 1 (=yes, 100% complete), 0 (=no, partially completed), 99(=care bundle not utilised) If the audit period is occurring before your centre has implemented the care bundle answer no for all cases.
DID THE PATIENT RECEIVE A FLUID BALANCE ASSESSMENT?	a) Definition: any one of: patient examination incorporating assessment of volume status (including euvolaemia), clinical impression that includes reference to volume status, treatment plan includes correction of over- or under-hydration b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)
DID PATIENT RECEIVE URINALYSIS AT THE TIME OF OR FOLLOWING AKI?	a) Definition: urinalysis (urine dipstick testing) results recorded in medical or nursing record b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known), 99(=not possible due to anuria). *Urinary ACR/PCR is not equivalent and should not be counted as an acceptable alternative, urinalysis occurring before onset of AKI should not be counted*
WAS THE PATIENT RECEIVING ANY OF THE FOLLOWING MEDICATIONS AT TIME OF AKI?	Yes(=1) or No(=0) for each of the following classes of medications: a) ACE inhibitors e.g. ramipril; lisinopril; trandolopril; enalapril; captopril etc. b) Angiotensin receptor blockers e.g. candesartan; irbesartan; losartan; telmisartan; olmesartan; valsartan etc. c) Non-steroidal anti-inflammatory drugs (NSAID) e.g. ibuprofen; diclofenac; naproxen; indomethacin, meloxicam etc. d) Mineralocorticoid receptor blockers e.g. spironolactone; eplenerone e) Loop diuretic e.g. frusemide, bumetanide f) Thiazide diuretic e.g. bendrofluazide; indapamide; hydrochlorothiazide g) Aminoglycoside e.g. gentamicin; amikacin h) Trimethoprim
DID THE PATIENT RECEIVE A MEDICATION REVIEW AT TIME OF OR AFTER AKI?	a) Definition: treatment plan includes cessation of relevant medication*, treatment plan includes avoidance of relevant medication, relevant medications stopped within 24hrs of first AKI warning stage result, documented pharmacy review b) Response options: 0 (=no), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known)

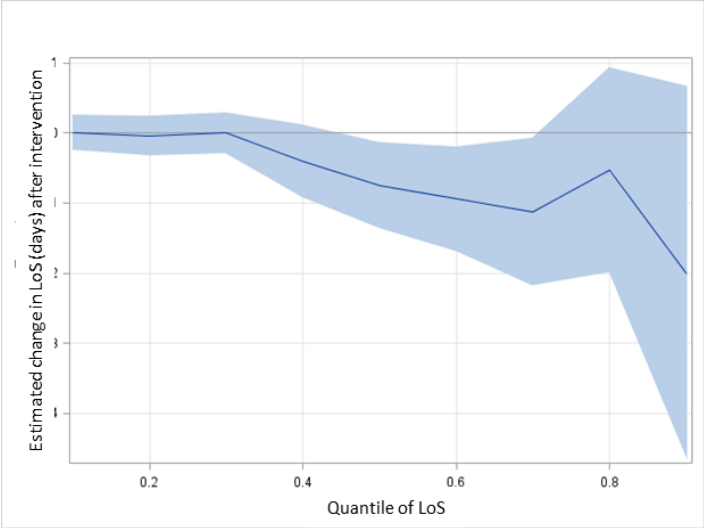
DID THE PATIENT RECEIVE RENAL IMAGING?	Not all AKI stage 1 patients need renal imaging, so score these patients as 'no AKI stage 1' a) Definition: renal ultrasound/CT/MRI imaging following onset of AKI b) Response options: 0 (=not done), 1 (=yes within <6hrs), 2 (=yes between 6-12hrs), 3 (=yes between 12-24hrs), 4 (yes between 24-48hrs), 5 (=yes >48hrs), 6 (=yes but timing not known) 98(=no AKI stage 1), 99(=not appropriate – AKI stage 1 or senior clinician decision)
DID THE PATIENT RECEIVE SPECIALIST INPUT?	Not all AKI stage 1 patients need renal imaging, so score these patients as 'no AKI stage 1/2' Specialist input may be advice or review by nephrology, critical care outreach team (CCOT) or intensive care teams, or transfer to nephrology unit, high dependency or intensive care unit. If more than one of these happened, score that corresponding to highest level of input (transfer > seen by > telephone advice). a) Definition: medical record contains documentation of telephone discussion with nephrology/ICU SpR or more senior, nephrology/ICU review or transfer to nephrology ward/ICU b) Response options: 1(=yes, discussion with nephrology), 2(=yes, seen by nephrology), 3(yes, discussion with ICU/outreach), 4(seen by ICU/outreach), 5(transfer to more specialist area; includes renal ward, high dependency or ICU), 0(=no), 99(=not appropriate – AKI stage 1/2 or senior clinician decision)
WAS PATIENT CATHETERISED AS PART OF AKI CARE?	Included as a balancing measuring (an increase in unnecessary urinary catheterization would be an unintended consequence) a) Definition: new urinary catheter placed as part of AKI management plan, or new urinary catheter placed within 48hrs of AKI onset b) Response options: Yes(=1 to relieve bladder outflow obstruction), Yes(=2 for any other reason including fluid balance monitoring), No(=0), Not possible(=99 e.g. long term catheter already in place, urinary diversion etc.)

	All		Frimley		Bradford		Ashford		LGI		LSJ	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
No. of AKI episodes	14042	10017	1562	4222	2195	2158	2733	1978	1601	631	5951	1028
% male	50.3%	48.1%	48.5%	46.7%	47.1%	48.6%	47.8%	47.7%	57.7%	56.1%	51.2%	48.7%
Age-group (%)												
18-59	23.1%	20.3%	15.5%	16.6%	26.1%	27.1%	15.1%	16.6%	25.6%	28.5%	27.0%	23.3%
60-69	15.7%	15.3%	12.4%	13.5%	18.4%	18.7%	12.3%	13.0%	15.9%	17.3%	17.1%	18.6%
70-79	23.7%	23.5%	24.5%	23.7%	24.4%	24.5%	21.3%	22.7%	26.3%	24.9%	23.5%	21.4%
80-89	27.2%	29.8%	32.7%	33.3%	23.9%	22.9%	35.7%	33.9%	24.9%	23.0%	23.7%	26.5%
90+	10.3%	11.1%	14.9%	12.9	7.2%	6.8%	15.6%	13.8%	7.3%	6.3%	8.7%	10.3%
Median age (years)	75.4	76.6	79.5	78.7	73.3	72.0	80.2	79.1	73.5	71.4	73.1	73.8
Co-morbidity score												
0	16.4%	18.8%	17.6%	19.8%	18.4%	20.5%	17.8%	18.1%	18.4%	18.9%	14.2%	12.7%
1	20.3%	21.0%	23.6%	22.2%	22.8%	21.1%	21.8%	20.9%	22.0%	20.6%	17.3%	15.7%
2	20.2%	19.4%	18.1%	18.9%	21.4%	20.3%	19.3%	19.0%	21.5%	19.7%	20.4%	20.5%
3+	43.1%	40.8%	40.7%	39.1%	37.5%	38.1%	41.2%	42.1%	38.1%	40.9%	48.1%	51.2%
Ethnicity												
Afro-Caribbean	1.4%	0.8%	0.4%	0.6%	1.1%	1.1%	0.5%	0.6%	1.7%	1.1%	2.0%	1.3%
South-Asian	5.5%	5.9%	0.7%	1.0%	18.8%	20.4%	1.8%	1.7%	4.8%	4.6%	3.7%	4.3%
Other	2.8%	2.8%	3.3%	2.6%	1.8%	2.0%	4.9%	4.9%	2.6%	2.4%	2.3%	1.6%
White	86.1%	85.3%	91.0%	91.5%	71.3%	69.3%	86.8%	86.3%	88.5%	87.0%	89.4%	90.4%
Missing	4.2%	5.2%	4.6%	4.3%	7.1%	7.1%	6.0%	6.6%	2.5%	4.9%	2.6%	2.4%
Deprivation												
1 (least)	23.6%	36.4%	57.4%	57.8%	3.9%	4.2%	46.8%	44.4%	14.9%	15.9%	13.6%	13.1%
2	17.8%	16.7%	18.2%	17.5%	8.7%	7.5%	21.2%	23.0%	19.9%	20.4%	18.9%	18.4%
3	16.0%	15.8%	15.1%	14.9%	13.4%	12.3%	20.6%	21.3%	14.2%	13.3%	15.5%	18.0%
4	15.7%	13.3%	7.4%	8.1%	25.1%	23.9%	10.8%	10.6%	17.0%	17.1%	16.4%	14.6%
5 (most)	26.8%	17.6%	1.7%	1.3%	48.9%	52.2%	0.3%	0.3%	33.7%	33.1%	35.5%	35.7%
Missing	0.1%	0.2%	0.2%	0.4%	0.1%	0%	0.3%	0.3%	0.4%	0.2%	0.1%	0.2%
30-day crude mortality	25.2%	23.9%	22.0%	21.5%	22.4%	23.9%	24.3%	26.4%	23.3%	21.2%	27.9%	30.1%
Peak AKI stage												
1	60.6%	64.5%	65.7%	67.1%	64.6%	62.7%	63.8%	64.7%	66.8%	69.3%	54.7%	54.5%
2	21.4%	19.8%	19.8%	19.2%	19.4%	20.3%	19.8%	19.8%	19.4%	17.0%	23.8%	23.2%
3	18.0%	15.7%	14.5%	13.7%	16.0%	17.1%	16.4%	15.5%	13.8%	13.8%	21.5%	22.3%
Hospital-acquired* (%)	53.8%	49.4%	55.4%	50.5%	46.8%	45%	47.8%	43.6%	72.6%	70.8%	53.7%	52.5%
Hospital length of stay (days, median, IQR)	10 (5-20)	9 (4-18)	10 (5-20)	9 (4-19)	8 (3-16)	7 (3-15)	9 (4-17)	8 (4-16)	13 (6-25)	11 (5-24)	11 (5-22)	11 (5-22)

S4 Table: Patient demographics in control and intervention periods at each hospital and overall.
There were some differences in catchment population of each hospital in terms of patient demographics, but no differences between control and intervention periods at a centre level.
Abbreviations: Ashford: Ashford and St Peter's Hospital; Bradford: Bradford Royal Infirmary; Frimley: Frimley Park Hospital; LGI: Leeds General Infirmary; LSJ: Leeds St James' Hospital.
* hospital acquired AKI defined as AKI onset >24hrs after hospital admission.

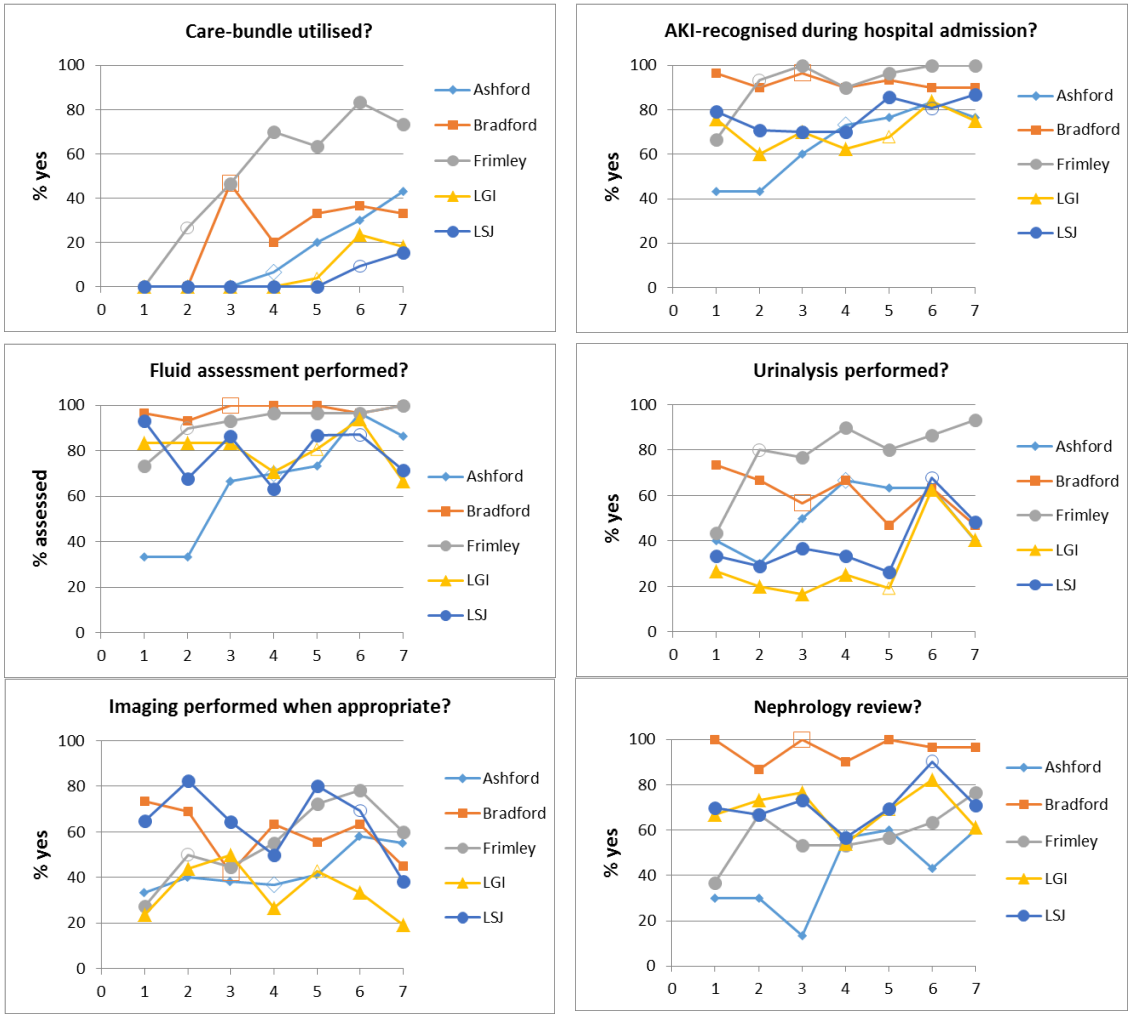
Multilevel logistic regression for AKI incidence				
	Odds ratio	**95% CI**		**p-value**
Intervention (reference=control): all cases	1.12	1.03	1.22	0.009
Intervention: AKI stage 1 only	*1.13*	*1.03*	*1.25*	*0.01*
Intervention: AKI stage 2 only	*1.12*	*0.98*	*1.27*	*0.08*
Intervention: AKI stage 3 only	*1.11*	*0.95*	*1.28*	*0.17*

S5 Table: Results of multilevel logistic regression for AKI incidence, overall and for each AKI stage
The effect size of an increase in AKI incidence with the intervention was very similar across all AKI stages; therefore a change in proportion of patients at different severities of AKI was not observed between control and intervention periods.



Quantile	Change in LoS (95% CI)	p-value	LoS at quantile (in days) control	intervention
0.1	0 (-0.3 - 0.3)	1	2	2
0.2	-0.04 (-0.3 - 0.2)	0.8	4	3
0.3	0 (-0.3 - 0.3)	1	6	5
0.4	-0.4 (-0.9 - 0.1)	0.13	8	7
0.5	-0.8 (-1.4 - -0.1)	0.02	10	9
0.6	-0.9 (-1.7 - -0.2)	0.01	13	11
0.7	-1.1 (-2.2 - -0.1)	0.04	17	15
0.8	-0.5 (-2.0 - 0.9)	0.48	24	21
0.9	-2 (-4.7 - 0.7)	0.14	36	32

S6 Figure: Quantile regression for change in hospital LoS (in days) with all patients included.
LoS is shown on the y-axis at different quantiles of the distribution, comparing the effect of the intervention against control period. The results are similar to the main analysis that included only those patients who survived to discharge. The solid line represents the estimated changes in LoS distribution quantiles from before to after the introduction of the intervention across the different quantiles of the distribution, and the shaded area represents 95% CI. Results show a reduced LoS during in intervention period (from quantiles 0.5 upwards, effect size and median LoS at individual quantiles shown in the table).



S7 Figure: Process measures presented individually per site.
Improvements were seen in care bundle utilisation, AKI recognition, fluid assessment and urinalysis rates. There were no differences in rates of renal imaging or specialist referral between control and intervention periods.

The x-axis shows the three-month periods sequentially throughout the study. Period 1 represents the baseline prior to any hospital introducing the intervention, periods 2-6 represent the intervention periods, and period 7 the post-implementation period with all hospitals exposed to the intervention.

For each hospital, the data point without shading shows the transition period at the start of implementation).

Abbreviations: Ashford: Ashford and St Peter's Hospital; Bradford: Bradford Royal Infirmary; Frimley: Frimley Park Hospital; LGI: Leeds General Infirmary; LSJ: Leeds St James' Hospital.